AMENDMENTS TO THE CLAIMS Docket No. PHUS-28

CLAIMS

We claim:

1) (Currently amended) A pharmaceutical composition comprising:
   a) a COX-II inhibitor, wherein the COX-II inhibitor binds COX-II receptors selectively over COX-I receptors or binds COX-II receptors specifically;
   b) a muscle relaxant; and
   c) at least one pharmaceutical excipient; wherein the COX-II inhibitor and muscle relaxant provide an additive or synergistic therapeutic effect when administered to a subject.
2) (Cancelled)
3) (Cancelled)
4) (Original) The pharmaceutical composition of claim 1, wherein the weight ratio of COX-II inhibitor to muscle relaxant varies from (12.5:2.2) to (50:8).
5) (Original) The pharmaceutical composition of claim 1, wherein the COX-II inhibitor is selected from the group consisting of central muscle relaxants and neuromuscular blocking agents.
6) (Original) The pharmaceutical composition of claim 1, wherein the at least one pharmaceutical excipient is independently selected from the group consisting of an acidifying agent, adsorbents, alkalizing agent, antioxidants, buffering agent, colorant, flavorant, sweetening agent, tablet antiadherent, tablet binder, tablet and capsule diluent, tablet direct compression excipient, tablet disintegrant, tablet glidant, tablet lubricant, tablet or capsule opaquant, plasticizer, surface active agent, solvent, oil, soap, detergent, and tablet polishing agent.
7) (Previously amended) The pharmaceutical composition of claim 1, wherein the muscle relaxant is selected from the group consisting of alcuronium, alosetron, aminophylline, baclofen, carisoprodol, chlorphenesin, chlorphenesin carbamate, chlorzoxazone, chlormezanone, cyclobenzaprine, dantrolene, decamethonium, diazepam, dyphylline, eperisione, ethaverine, gallamine triethiodide, hexafluorenium, mephenesin, metaxalone, methocarbamol, metocurine iodide, orphenadrine, pancuronium, papaverine, pipecuronium, pridinol, succinylcholine, theophylline, tizanidine, tolperisone, tubocurarine, vecuronium, idrocilamide, ligustilide, cnidilide, and senkyunolide.
8) (Thrice Amended) The pharmaceutical composition of claim 1, wherein the COX-II inhibitor is selected from the group consisting of rofecoxib, celecoxib, flosulide, ~~[NS-398]~~ N-(2-

cyclohexyloxy-4-nitrophenyl) methanesulfonamide, [~~DUP-697~~] 5-bromo-2-(4-fluorophenyl)-3-(4-methylsulfonyl) thiophene, meloxicam, 6-methoxy-2-naphthylacetic acid, nabumetone, etodolac, nimesulide, [~~SC-57666~~] 1-fluoro-4-(2-(4-(methylsulfonyl)-phenyl)-1-cyclopenten-1-yl)-benzene, [~~T-614~~] N-(3-formylamino-4-oxo-6-phenoxy-4H-chromen-7-yl) methanesulfonamide, and combinations thereof.

9) (Canceled)

10) (Currently amended) A pharmaceutical dosage form comprising:

a) a therapeutically effective amount of a COX-II inhibitor, wherein the COX-II inhibitor binds COX-II receptors selectively over COX-I receptors or binds COX-II receptors specifically;

b) a therapeutically effective amount of a muscle relaxant; and

c) at least one pharmaceutical excipient.

11) (Original) The pharmaceutical dosage form of claim 10, wherein the dosage form is selected from the group consisting of a gel, cream, ointment, pill, tablet, capsule, liquid, suspension, osmotic device, bead, granule, spheroid, particulate, paste, prill, reconstitutable solid, powder, and injectible liquid.

12) (Twice amended) The pharmaceutical dosage form of claim 10, wherein the [~~dosage form independently provides a controlled, delayed, sustained, immediate, timed, slow or rapid release of each of the~~] COX-II inhibitor is released at a faster rate than [~~and~~] the muscle relaxant, the COX-II inhibitor is released at a slower rate than the muscle relaxant, or the COX-II inhibitor is released at approximately the same rate as the muscle relaxant when the dosage form is [~~when~~] exposed to an aqueous environment.

13) (Previously amended) The pharmaceutical dosage form of claim 10, wherein the dosage form provides therapeutically effective plasma levels of the COX-II inhibitor for a period up to at least about 12 hours after administration to a subject.

14) (Previously amended) The pharmaceutical dosage form of claim 10, wherein after administration to a subject the dosage form provides therapeutically effective plasma levels of the muscle relaxant for a period of administration sufficient to enhance the therapeutic benefit provided by the COX-II inhibitor.

15) (Original) The pharmaceutical dosage form of claim 10, wherein the pharmaceutical dosage form is adapted for oral, buccal, ocular, otic, gastrointestinal, dermal, rectal, vaginal, cervical,

intrauterine, epidermal, transdermal, implant, mucosal, parenteral, sublingual, nasal, or pulmonary delivery.

16) (Previously amended) The pharmaceutical dosage form of claim 10, wherein the muscle relaxant is selected from the group consisting of alcuronium, alosetron, aminophylline, baclofen, carisoprodol, chlorphenesin, chlorphenesin carbamate, chlorzoxazone, chlormezanone, cyclobenzaprine, dantrolene, decamethonium, diazepam, dyphylline, eperisione, ethaverine, gallamine triethiodide, hexafluorenium, mephenesin, metaxalone, methocarbamol, metocurine iodide, orphenadrine, pancuronium, papaverine, pipecuronium, pridinol, succinylcholine, theophylline, tizanidine, tolperisone, tubocurarine, vecuronium, idrocilamide, ligustilide, cnidilide, and senkyunolide.

17) (Thrice amended) The pharmaceutical dosage form of claim 10, wherein the COX-II inhibitor is selected from the group consisting of rofecoxib, celecoxib, flosulide, [~~NS-398~~] N-(2-cyclohexyloxy-4-nitrophenyl) methanesulfonamide, [~~DUP-697~~] 5-bromo-2-(4-fluorophenyl)-3-(4-methylsulfonyl) thiophene, meloxicam, 6-methoxy-2-naphthylacetic acid, nabumetone, etodolac, nimesulide, [~~SC-57666~~] 1-fluoro-4-(2-(4-(methylsulfonyl)-phenyl)-1-cyclopenten-1-yl)-benzene, [~~T-614~~] N-(3-formylamino-4-oxo-6-phenoxy-4H-chromen-7-yl) methanesulfonamide, and combinations thereof.

18) (Twice amended) The pharmaceutical dosage form of claim 10, wherein [~~each drug is released rapidly and~~] the dosage form provides therapeutically effective levels of each drug for a period of at least 12 hours after administration to a subject.

19) (Original) The pharmaceutical dosage form of claim 18, wherein the period is about 12 to 60 hours.

20) (Original) The pharmaceutical dosage form of claim 19, wherein the period is about 12 to 30 hours.

21) (Original) The pharmaceutical dosage form of claim 19, wherein the period is about 18 to 48 hours.

22) (Previously amended) The pharmaceutical dosage form of claim 10, wherein after administration to a subject the plasma level of the COX-II inhibitor or muscle relaxant is dependent upon the plasma level of the muscle relaxant or COX-II inhibitor, respectively.

23) (Previously amended) The pharmaceutical dosage form of claim 10, wherein after administration to a subject the plasma level of the COX-II inhibitor or muscle relaxant is independent of the plasma level of the muscle relaxant or COX-II inhibitor, respectively.

24) (Original) The pharmaceutical dosage form of claim 10, wherein the dosage form provides therapeutic plasma levels for the muscle relaxant in an amount sufficient to provide a therapeutic benefit to a subject to whom it is administered.

25) (Previously amended) The pharmaceutical dosage form of claim 10, wherein after administration to a subject the dosage form provides therapeutic plasma levels for the COX-II inhibitor in the range of about 90 ng to about 300 ng per ml of plasma in the subject.

26) (Previously amended) The pharmaceutical dosage form of claim 10, wherein the COX-II inhibitor and muscle relaxant are released sequentially after exposure to an aqueous environment.

27) (Previously amended) The pharmaceutical dosage form of claim 10, wherein the COX-II inhibitor and muscle relaxant are released concurrently after exposure to an aqueous environment.

28) (Previously amended) The pharmaceutical dosage form of claim 10, wherein the COX-II inhibitor and muscle relaxant are released in spaced apart periods of time after exposure to an aqueous environment.

29) (Twice amended) The pharmaceutical dosage form of claim 10, wherein each drug is independently released according to a [~~rapid, immediate,~~] controlled, sustained, [~~slow,~~] timed, targeted, pseudo-first order, first order, pseudo-zero order, or zero-order[~~, and/or delayed~~] release profile after exposure to an aqueous environment, optionally wherein the release of one or both of the drugs begins after expiration of a lag period, and optionally wherein the release of one drug begins after release of the other drug has begun.

30) (Previously amended) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a controlled release of the COX-II inhibitor and a controlled release of the muscle relaxant after exposure to an aqueous environment.

31) (Twice amended) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a controlled release of the COX-II inhibitor after exposure to an aqueous environment and a [~~rapid~~] release of the muscle relaxant within two hours after exposure to an aqueous environment.

32) (Twice amended) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a controlled release of the muscle relaxant after exposure to an aqueous environment and a [~~rapid~~] release of the COX-II inhibitor within two hours after exposure to an aqueous environment.

33) (Twice amended) The pharmaceutical dosage form of claim 10, wherein the dosage form [~~provides a rapid release of~~] releases the COX-II inhibitor and [~~of~~] the muscle relaxant within two hours after exposure to an aqueous environment.

34) (Twice amended) The pharmaceutical dosage form of claim 10, wherein the dosage form [~~provides a rapid release of~~] releases the muscle relaxant within two hours after exposure to an environment of use and [~~a delayed but rapid~~] release of the COX-II inhibitor begins after [~~exposure to an aqueous environment~~] release of the muscle relaxant has begun.

35) (Twice amended) The pharmaceutical dosage form of claim [~~10~~] 34, wherein the dosage form provides a [~~rapid release of the muscle relaxant and a timed but~~] controlled release of the COX-II inhibitor after exposure to an aqueous environment.

36) (Twice amended) The pharmaceutical dosage form of claim 10, wherein the dosage form [~~provides a rapid release of~~] releases the COX-II inhibitor within two hours after exposure to an environment of use, [and a delayed but rapid] release of the muscle relaxant begins after [exposure to an aqueous environment] release of the COX-II inhibitor has begun.

37) (Twice amended) The pharmaceutical dosage form of claim [~~10~~] 36, wherein the dosage form provides a [~~rapid release of the COX-II inhibitor and a timed but~~] controlled release of the muscle relaxant after exposure to an aqueous environment.

38) (Original) The pharmaceutical dosage form of claim 10, wherein the weight ratio of COX-II inhibitor to muscle relaxant varies from 12.5:2.2 to 50:8.

39) (Canceled)

40) (Twice amended) A pharmaceutical composition comprising:

a) a COX-II inhibitor selected from the group consisting of rofecoxib, celecoxib, flosulide, [~~NS-398~~] N-(2-cyclohexyloxy-4-nitrophenyl) methanesulfonamide, [~~DUP-697~~] 5-bromo-2-(4-fluorophenyl)-3-(4-methylsulfonyl) thiophene, meloxicam, 6-methoxy-2-naphthylacetic acid, nabumetone, etodolac, nimesulide, [~~SC-57666~~] 1-fluoro-4-(2-(4-(methylsulfonyl)-phenyl)-1-cyclopenten-1-yl)-benzene, [~~T-614~~] N-(3-formylamino-4-oxo-6-phenoxy-4H-chromen-7-yl) methanesulfonamide, and combinations thereof;

b) a muscle relaxant selected from the group consisting of alcuronium, alosetron, aminophylline, baclofen, carisoprodol, chlorphenesin, chlorphenesin carbamate, chlorzoxazone, chlormezanone, cyclobenzaprine, dantrolene, decamethonium, diazepam, dyphylline, eperisione, ethaverine, gallamine triethiodide, hexafluorenium, mephenesin, metaxalone, methocarbamol, metocurine iodide, orphenadrine, pancuronium, papaverine, pipecuronium, pridinol, succinylcholine, theophylline, tizanidine, tolperisone, tubocurarine, vecuronium, idrocilamide, ligustilide, cnidilide, and senkyunolide and combinations thereof; and

c) at least one pharmaceutical excipient.

41) (Previously added) The composition of claim 40, wherein the at least one pharmaceutical excipient is independently selected from the group consisting of an acidifying agent, adsorbent, alkalizing agent, antioxidant, buffering agent, colorant, flavorant, sweetening agent, tablet antiadherent, tablet binder, tablet and capsule diluent, tablet direct compression excipient, tablet disintegrant, tablet glidant, tablet lubricant, tablet or capsule opaquant, plasticizer, surface active agent, solvent, oil, soap, detergent, and tablet polishing agent.

42) (Previously added) The composition of claim 41, the weight ratio of COX-II inhibitor to muscle relaxant varies from (12.5:2.2) to (50:8).

43) (Amended) The composition of claim 40, wherein the COX-II inhibitor and muscle relaxant are independently provided in each occurrence in controlled release form, sustained release form, [immediate,] timed release form, [~~slow or rapid release form~~] or in a form wherein complete release of drug occurs within two hours of beginning of its release.

44) (Amended) The composition of claim 43, wherein release of at least one of the COX-II inhibitor and muscle relaxant [~~are independently further provided in each occurrence in delayed or targeted release form~~] begins after expiration of a lag period and/or release of at least one of the COX-II inhibitor and the muscle relaxant is targeted in a subject to which the composition is administered.

45) (Previously added) The composition of claim 40, wherein at least one of the COX-II inhibitor and muscle relaxant are independently provided in each occurrence in pseudo-first order, first order, pseudo-zero order, or zero order release form.

46) (Previously added) A pharmaceutical dosage form comprising the pharmaceutical composition of claim 40.

47) (Previously added) A pharmaceutical dosage form comprising the pharmaceutical composition of claim 41.

48) (Previously added) A pharmaceutical dosage form comprising the pharmaceutical composition of claim 42.

49) (Previously added) A pharmaceutical composition comprising:

a) a COX-II inhibitor selected from the group consisting of rofecoxib and celecoxib;

b) pridinol; and

c) at least one pharmaceutical excipient.

50) (Previously added) The pharmaceutical composition of claim 49, wherein the at least one pharmaceutical excipient is independently selected from the group consisting of an acidifying agent, adsorbent, alkalizing agent, antioxidant, buffering agent, colorant, flavorant, sweetening agent, tablet antiadherent, tablet binder, tablet and capsule diluent, tablet direct compression excipient, tablet disintegrant, tablet glidant, tablet lubricant, tablet or capsule opaquant, plasticizer, surface active agent, solvent, oil, soap, detergent, and tablet polishing agent.

51) (Previously added) The composition of claim 49, the weight ratio of COX-II inhibitor to pridinol varies from (12.5:2.2) to (50:8).

52) (Amended) The composition of claim 49, wherein the COX-II inhibitor and pridinol are independently provided in each occurrence in controlled release form, sustained release form, [immediate,] timed release form, [~~slow or rapid release form~~] or in a form wherein complete release of drug occurs within two hours of beginning of its release.

53) (Amended) The composition of claim 52, wherein release of at least one of the COX-II inhibitor and pridinol [~~are independently further provided in each occurrence in delayed or targeted release form~~] begins after expiration of a lag period and/or release of at least one of the COX-II inhibitor and pridinol is targeted in a subject to which the composition is administered.

54) (Previously added) The composition of claim 49, wherein at least one of the COX-II inhibitor and pridinol are independently provided in each occurrence in pseudo-first order, first order, pseudo-zero order, or zero order release form.

A third composition (forming a drug-containing coat) was prepared by mixing rofecoxib (50.00 g), microcrystalline cellulose (250.00 g), lactose monohydrate (177.6 g), corn starch (57.00 g) and povidone (25.00 g). This mixture was wetted with a mixture of alcohol (96°, 100.00 ml) and Polysorbate 20 (1.60 g). This wet mixture was then granulated and dried at 40-50°C for 3 hours. The dried granulate was screened and mixed with colloidal silicon dioxide (4.10 g). This mixture was mixed to homogeneity with magnesium stearate (4.70 g). This final mixture was then compressed about the inert coat using biconcave 14.50 mm diameter punches. The coat had a final weight of about 570.0 mg and a hardness of about 7-12 kP.

A final composition (for forming the finish coat) was prepared by mixing HPMC 2910 (12.10 g), PEG 6000 (3.41 g), and titanium dioxide (4.48 g) in a mixture of methylene chloride and alcohol (96°) (70:30 v/v). The final composition was sprayed onto the drug-containing coat in a conventional pan coater to obtain film-coated tablets which membranes weigh about 20 mg.

In one embodiment the weight ratio of COX-II inhibitor to muscle relaxant varies from (12.5:2.2) to (50:8). In one embodiment, the dosage form provides therapeutic plasma levels for the COX-II inhibitor in the range of about 90 ng to about 300 ng per ml of plasma in a subject after administration to the subject.

The above is a detailed description of particular embodiments of the invention. It is recognized that departures from the disclosed embodiments may be made within the scope of the invention and that obvious modifications will occur to a person skilled in the art. Those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed herein and still obtain a like or similar result without departing from the spirit and scope of the invention. All of the embodiments disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure.